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Pretreatment with taurine prevented brain injury and exploratory behaviour associated with administration of anticancer drug cisplatin in rats

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ABSTRACT

The neurotoxicity associated with cisplatin treatment is one of the major side effects compromising the efficacy of the anti-cancer treatment. The present study investigated the possible protective effects of taurine, an intracellular amino acid, on cisplatin-induced brain injury and exploratory behaviour using five groups of ten female rats each. Group I received drinking water only. Group II orally received taurine alone at 200 mg/kg whereas Group III received cisplatin alone intraperitoneally at 10 mg/kg. Groups IV and V were treated with taurine at 100 and 200 mg/kg respectively for sixteen consecutive days and a single intraperitoneal injection of cisplatin on day 13 to induce neurotoxicity. Endpoint analyses using video-tracking software revealed that cisplatin administration alone caused neurobehavioral deficits evinced by marked decrease in the total distance travelled, average speed, total time mobile, total mobile episode, number of crossing and absolute turn angle. Furthermore, cisplatin alone significantly suppressed brain antioxidant defense mechanisms, elevated nitric oxide and lipid peroxidation levels whereas it increased acetylcholinesterase activity in the treated rats. However, rats pretreated with taurine exhibited significant improvement in behavioural performance and brain antioxidant status with concomitant decrease in acetylcholinesterase activity and oxidative stress indices when compared with cisplatin alone group. Histologically, taurine pretreatment prevented cisplatin-induced neuronal death in the cerebral and cerebellar cortices, caudo-putamen and hippocampus as well as abrogated cisplatin-mediated decrease in the dendritic arborization and mean diameter of the somata of pyramidal neurons in the treated rats. In conclusion, taurine may be a possible protective supplement to reduce cisplatin-induced side-effects including neurotoxicity in patients undergoing cisplatin treatment.

1. Introduction

Cis-diamminedicholoroplatinum (Cisplatin) is a chemotherapeutic agent used to treat solid tumours of children and adults. Cisplatin has a wide spectrum of use in various tumor events, including the lung, kidney, ovary, testis, bladder, head, neck, and endometrium (Pabla and Dong 2008). Despite the satisfactory anti-cancer efficacy, cisplatin chemotherapy is associated with serious side effects such as neurotoxicity [1–3]. Indeed, cisplatin-induced neurotoxicity often lead to dose reduction or early cessation of chemotherapy which consequently affects patient life [4, 5]. Cisplatin reportedly penetrated into the human brain resulting in a significant concentration of cisplatin in the cerebrospinal fluid [6]. Moreover, Cisplatin reportedly elicited neurotoxicity via mechanisms involving increased reactive oxygen species production, 8-oxoguanine DNA damage, inflammation, mitochondrial dysfunction, and apoptosis in the nervous system [7–10].

Unfortunately, there is no standard clinical method for the early detection and comprehensive assessment of cisplatin-induced neurotoxicity presently known [11]. The American Society of Clinical Oncology is currently concerned about developing a guideline for the prevention and treatment of chemotherapy-induced neuropathies in cancer survivors [12]. Thus, the understanding of the mechanisms by which cisplatin triggers neurological damage is essential for improving approaches to therapeutic interventions. Since oxidative damage associated with the side effects of cisplatin can be ameliorated or mitigated by anti-oxidative [9,13], this study considered the use of a compound, taurine, reported to possess anti-oxidative, anti-inflammatory and anti-apoptotic properties to mitigate cisplatin-induced toxicity in brain of rats.

Taurine (2-aminoethanesulfonic acid) is a free intracellular amino acid, present in high concentrations in the mammalian brain and can be ingested especially from sea foods [14]. The biosynthesis of taurine in human occurs primarily in the liver via oxidation and decarboxylation of the amino acid, cysteine [15]. Taurine reportedly crosses the blood –

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brain barrier [16,17]. It has been reported to ameliorate cognitive dysfunction and neuronal deficits in diabetic rats [18,19]. Taurine protected against neuroinflammation and white matter injury following intracerebral hemorrhage in rats [20]. It has been reported to play a protective role against cadmium and fluoride-induced neurotoxicity [21,22]. Recent studies demonstrated the chemoprotective effects of taurine on cisplatin-induced cardiotoxicity and renal injury via modulation of inflammation and oxidative damage [23,24].

Hitherto, there is no study in literature on the role of taurine in cisplatin-induced brain damage and alterations in neurobehavioral characteristics namely the locomotor and exploratory profiles in rats. The rationale of the present study was to investigate the efficacy of taurine in the management of cisplatin-induced neurotoxicity. The present study investigated, for the first time, the effectiveness of taurine in preventing cisplatin-induced brain injury and neurobehaviour deficits in Wistar rats by assessing novelty-associated behavioral stress responses with the aid of video-tracking software (ANY-maze, Stoelting CO, USA). Subsequently, oxidative stress indices, acetylcholinesterase (AChE) and antioxidant enzyme activities as well as histopathological examination of the brain tissues were explored to further gain mechanistic insight into how taurine possibly prevents brain toxicity in rats administered with anticancer drug cisplatin.

2. Materials and methods

2.1. Chemicals

Cisplatin (Korea United Pharm. Inc., Naojang, Korea), taurine (2-aminoethanesulfonic acid), epinephrine, 5′, 5′-dithiobis(2-nitro-benzoic acid), reduced glutathione, 1-chloro-2,4-dinitrobenzene and thiobarbituric acid were purchased from Sigma Chemical Co. (St Louis, MO, USA). All other reagents were of analytical grade and purchased from the British Drug Houses (Poole, Dorset, UK).

2.2. Animal model

Fifty adult female Wistar rats, weighing 90–125 g, were obtained and housed in a 12 h light/ dark cycle and well-ventilated plastic cages (10 animals in each) in the animal house of the Department of Veterinary Physiology, University of Ibadan, Nigeria. They were allowed access to rat pellets and water *ad libitum* for two weeks acclimatization before experiment. All the animals received humane care according to the conditions stated in the 'Ethics Guiding the Care and Use of Laboratory Animals' obtained from the University of Ibadan Ethical Committee. Chemotherapy involves the use of drugs including cisplatin for cancer treatment in both male and female patients. Hence, to mimic true life exposure situation in female, we performed the present study using female rats.

2.3. Experimental design

Animals were randomly allocated to 5 groups of 10 rats each and were treated for 16 consecutive days as follows:

Group I: Rats received drinking water only orally for 16 consecutive days.

Group II: Rats were orally administered taurine (TAU, 200 mg/kg) for 16 consecutive days.

Group III: Rats were administered single dose of cisplatin (CIS, 10 mg/kg, i.p.) on day 13.

Group IV: Rats were daily administered with taurine (TAU 1, 100 mg/ kg, orally) for 16 consecutive days and a single dose of cisplatin (CIS, 10 mg/kg, i.p) on day 13.

Group V: Rats were daily administered with taurine (TAU 2, 200 mg/ kg, orally) for 16 consecutive days and a single dose of cisplatin (CIS, 10 mg/kg, i.p) on day 13.

Stock solution of taurine (100 mg/mL) using drinking water as a vehicle was prepared fresh every other day. The doses of taurine and cisplatin used in the present investigation were chosen based on the previously published data [22, 25]. Taurine was administered for 12 consecutive days before the cisplatin to facilitate the bioavailability of the antioxidant as well as augmentation of the anti-oxidative capacity of the animals at the time of cisplatin exposure. The administration of cisplatin on day 13 prior to sacrifice of the animals on day 17 was to ensure its bioavailability to cause significant brain injury or neurotoxic effects, thereby revealing the efficacy of taurine in preventing cisplatin-mediated neurotoxicity.

2.4. Behavioral assessment

Behavioral assessment of the rats was performed 24 hours after the last treatment between 10:00 a.m. and 4:00 p.m. according to a standard procedure [26]. Briefly, each rat from the experimental groups was allowed to freely explore the novel apparatus (wooden box of 56 cm width × 56 cm length × 20 cm height). The floor of the apparatus was divided into sixteen evenly spaced squares (14 × 14 cm) by lines with four squares in the center of the apparatus. The behavior of the rats was filmed during a 7-minute trial using a webcam (DNE webcam, Porto Alegre, Brazil) mounted above the apparatus and attached to a laptop. The behavioral parameters were automatically calculated at a rate of 30 frames per second using video-tracking software (ANY-maze, Stoelting CO, USA).

2.5. Evaluation of locomotor, motor and exploratory activities

Assessment of the locomotor and motor patterns of the experimental rats was performed by evaluating the total distance travelled, total time mobile, average speed, total time episode, absolute turn angle and number of crossing. Analysis of the exploratory profile of the rats was performed using representative track plots in order to evaluate the exploratory activity in the novel environment. The exploratory activities of the rats in the novel environment were measured using representative track plots automatically generated from the video-tracking software (ANY-maze, Stoelting CO, USA).

2.6. Assessment of brain antioxidant status

Ten (10) rats in each group were sacrificed subsequent to the behavioral tests. Five rats were euthanized by transcardiac perfusion with 10% neutral buffer formalin for histological analysis whereas the remaining five rats were euthanized by cervical dislocation and processed for biochemical assays. The cranium was opened and the brain was carefully excised according to established method [27]. The brain samples were homogenized in four volumes of phosphate buffer (pH 7.4) and the resulting homogenate was centrifuged at 10,000 xg for 15 min at 4 °C to obtain the supernatant which was used to assay for oxidative stress indices, acetylcholinesterase and antioxidant enzyme activities. Protein concentration was assayed according to the method described by Bradford [28].

2.7. Determination of acetylcholinesterase activity

The brain acetylcholinesterase activity was assayed according to the method of Ellman et al. [29]. Briefly, the assay mixture consisted of 135 µL of distilled water, 20 µL of 100 mM potassium phosphate buffer (pH 7.4), 20 µL of 10 mM DTNB, 5 µL of diluted sample (1:10 v/v), and 20 µL of 8 mM acetylthiocholine as a substrate. The degradation of acetylthiocholine iodide was analyzed for 5 min (30 s intervals) at 412 nm using a SpectraMax plate reader (Molecular Devices, CA, USA) and the results were expressed as µmol/min/mg protein.